UNITED STATES ENVIRONMENTAL PROTECTION AGENCY
WASHINGTON, D.C. 20460

OFFICE OF CHEMICAL SAFETY AND POLLUTION PREVENTION

MEMORANDUM

Date: January 8, 2013

SUBJECT: **Dinotefuran**: Data Evaluation Record for Dinotefuran: Characterization of the Temporal Transferability of Dinotefuran Residues on Cotton Gloves Following Topical Application to Dogs Using an Equilibrium Loading-Based Petting Simulation

PC Code: 044312
Decision No.: 463938
Petition No.: NA
Risk Assessment Type: NA
TXR No.: NA
MRID No.: 48787102

DP Barcode: D401351
Registration No.: 83399-6
Regulatory Action: Data Evaluation Record
Case No.: NA
CAS Nos.: 165252-70-0
40 CFR: §180.603

FROM: Barry O'Keefe, Senior Biologist
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THROUGH: Jeff Dawson, Acting Branch Chief
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TO: Rita Kumar, Senior Regulatory Specialist
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This document serves as a data evaluation record for the dinotefuran exposure study, "Characterization of the Temporal Transferability of Dinotefuran Residues on Cotton Gloves Following Topical Application to Dogs Using an Equilibrium Loading-Based Petting Simulation (MRID 48787102)", submitted by Ceva Animal Health in support of the registration Ceva Animal Health Vectra for Dogs and Puppies™. Ceva Animal Health submitted this study as a required condition of registration. The study was conducted to measure the amount of dinotefuran that may be dislodged from dog's hair coat after single treatment of this spot-on product. A primary review of this study was conducted by Versar, Inc. under the guidance of HED.

DATA EVALUATION RECORD

STUDY TYPE: Transferable Residues After Petting Simulations to Treated Animal Hair

TEST MATERIAL: The test material was Ceva Animal Health Vectra for Dogs & Puppies™, a spot-on formulation containing 22% dinotefuran and 3% pyriproxyfen as the active ingredients.

SYNONYMS: Dinotefuran; CAS 165252-70-0

CITATION:

Study Author/Director:	Megan T. Boatwright Robert J. Testman
Title:	Characterization of the Temporal Transferability of Dinotefuran Residues on Cotton Gloves Following Topical Application to Dogs Using an Equilibrium Loading-Based Petting Simulation
Report Date:	March 16, 2012
Performing Laboratory:	Golden Pacific Laboratories, LLC (GPL) 4720 W. Jennifer Ave., Suite 105 Fresno, California 93722
Identifying Codes:	Sponsor Study No. SVP09006b; GPL Study No.: 100340; MRID 48787102

SPONSOR: Ceva Animal Health
301 Route 17 North
Rutherford, NJ 07070

EXECUTIVE SUMMARY:

This review analyzes the report "*Characterization of the Temporal Transferability of Dinotefuran Residues on Cotton Gloves Following Topical Application to Dogs Using an Equilibrium Loading-Based Petting Simulation*" submitted by Ceva Animal Health. The purpose of the study was to measure the transferability of the test substance, a spot-on formulation of dinotefuran, over time from the haircoat of treated dogs to a gloved hand.

The test substance used was Ceva Animal Health Vectra for Dogs & Puppies™ which contains 22% dinotefuran and 3% pyriproxyfen. The test substance, provided in ready-to-use application tubes, was administered to 24 dogs within 8 treatment groups (3 dogs per group). The product was topically applied to each dog at three spots on each dog's back, beginning between the shoulder blades. An entire tube (4 ml product) was used on each dog, resulting in application rates ranging from 935 to 1003 mg ai/dog. Transferred dinotefuran residues on treated dog hair were measured after stroking the dog ninety times (30 petting simulations of 3 strokes each) with a mannequin hand fitted with three cotton gloves over top of a nitrile glove. Treatment groups 1 through 8 were sampled at separate intervals of 4 hrs, 12 hrs, 1, 2, 4, 7, 14 and 28 days after application, respectively. Each dog was sampled only once after application, in addition to the day before application.

Measured dinotefuran residues (µg/glove) were corrected by Versar using the average laboratory recovery from the fortification level closest to the field residue (91% for residues <5,000 µg/sample, 97% for residues 5,000 to 55,000 µg/sample, and 90% for residues >55,000 µg/sample). When residues were

reported as less than the limit of quantitation (LOQ), which was 1 µg/glove, Versar used a finite value of ½ LOQ (0.5 µg/glove). Versar also calculated residues in µg/cm^2 of total dog surface area and the percentage of the applied dose that was transferable.

Average dinotefuran residue from petting simulations conducted 4 hours after application was 70,427 µg/glove (7.12% of applied dose). Residues decreased with increasing time between the test product application and dislodgeability sampling. At the Day 28 interval, the average dinotefuran residues were 500 µg/glove (0.05% of applied dose) and the inner glove residues were <LOQ.

Versar performed a dissipation kinetics analysis for dinotefuran based on the percentage of original application dose transferred, as natural logarithms. Using the individual data points for percentage of applied dose transferable vs. time for samples collected from 4 hours through day 28 after application, the half-life calculated by Versar was 4.2 days (R^2 = 0.858).

The following issues of concern are noted:

- The Study did not follow 2 of the recommendations outlined by EPA in the protocol review dated November 17, 2009 (D368147, 11/17/09, B. O'Keefe). Note that in an announcement on the Summit VetPharm (SVP) website, it was announced that in 2010 CEVA acquired Summit VetPharm LLC.

    - HED recommended that SVP include a petting simulation within the first hour after treatment; e.g. at 30 minutes after treatment for an acute/slick test. In the actual field study, the first petting simulation after dosing took place 4 hours after treatment. *Note: In a subsequent meeting with Summit VetPharm HED agreed to the first petting simulation occurring at 4 hours after treatment.*
    - HED recommended that SVP consider the dog's health and their ability to remove product residue in the label and protocol directions. As stated in the submitted protocol, "whenever possible, dosing should be restricted to areas that would be difficult for the dog to reach and generally inaccessible for grooming purposes (i.e., intrascapular). *Instead*, the application of test substance in the field took place at three spots along the dogs back (intrascapular to back of tail area). According to the HED protocol review "If applied at three spots, the dogs may be able to lick and remove the mid-back and base of tail application points." *Note: In a subsequent meeting with Summit VetPharm HED agreed to allow the three spot application procedure.*

- The mannequin hand was clothed in three cotton gloves and one nitrile glove. Rinse samples of the chemical resistant gloves were not collected. Absorbency data were not presented to quantify transfer through the three cotton gloves or to examine the difference between cotton gloves and bare hands.

- Field fortification samples or travel recovery samples were not prepared. The Registrant did, however, submit a storage stability study (GPL Study 100338) which demonstrated the stability of dinotefuran in cotton glove samples for up to 6 months of frozen storage. Additionally, laboratory recovery samples were analyzed with each analytical set.

- The Registrant did not correct the residues for storage stability or laboratory recovery. Versar corrected the results for average laboratory recoveries.

- The characteristics of the mannequin hand were not reported, such as type of plastic and surface area.

- The amount of pressure applied to the mannequin hand was not reported.
- No information was provided on the fate of the product once it is applied. The samples were analyzed for dinotefuran only.
- The Submitter did not sign the GLP Compliance Statement of the Study Report.

COMPLIANCE: Signed and dated GLP, Quality Assurance, and Data Confidentiality statements were provided. The study sponsor waived claims of confidentiality within the scope of FIFRA Section 10(d) (1) (A), (B), or (C). The study sponsor and director stated that the analytical phase of the study was conducted under EPA Good Laboratory Practice Standards (40 CFR part 160), but the field phase at Young Veterinary Research Services (YVRS) was not conducted under GLPs.

CONCURRENT EXPOSURE STUDY: No

WAS AIR SAMPLING CONDUCTED IN CONJUNCTION WITH SURFACE SAMPLING? No

GUIDELINE OR PROTOCOL FOLLOWED: The study was reviewed using applicable sections of the OPPTS Test Guidelines Series 875, Occupational and Residential Exposure Test Guidelines, Group B: 875.2100 (dislodgeable foliar residue), 875.2300 (indoor surface residue) and 875.2400 (dermal exposure). A compliance checklist is provided in Appendix A.

I. MATERIALS AND METHODS

A. MATERIALS

1. Test Material:

Active ingredient:	Dinotefuran
Formulation:	Ceva Animal Health Vectra for Dogs & Puppies™; Spot-on formulation containing 22% dinotefuran. The product also contains 3% pyriproxyfen, but this active ingredient was not analyzed in the study.
Purity technical:	99.37% (expires 08/18/2013)
Purity formulation:	22.21%
Lot # technical:	K08B3569
Lot # formulation:	0222601
CAS #(s):	165252-70-0
Other Relevant Information:	EPA Registration 83399-10

2. Relevance of Test Material to Proposed Formulation(s):

The test material appears to be the same as the product described on the label for EPA Registration 83399-10 (approved March 5, 2009, obtained from PPLS). However, the product name on the label is SVP9, which is different than the product name used in this study.

B. STUDY DESIGN

The study was conducted according to procedures described in the Study Protocol (Sponsor Study No. SVP09006b; GPL Study Number 100340), and associated amendments or deviations. The protocol was reviewed by EPA (DP387315, 7/6/11, B. O'Keefe and D368147, 11/17/09, B. O'Keefe).

There was one amendment to the protocol and one deviation from the protocol. The amendment involved adding the identity of the reference substance. The deviation involved using a dog that weighed 20.3 lbs, which is outside the range specified in the protocol (21 to 55 lbs). The deviation occurred because there was an insufficient number of dogs that met the protocol criteria. According to the study, the use of one dog at a weight of 20 lbs. has the potential to slightly increase the transferability for that dog, but is not expected to impact the study conclusions.

1. Site Description:

Test location: The study was conducted at Young Veterinary Research Services (YVRS) in Turlock, California. The animals were housed in cages within a sheltered facility with cement floors. Currently acceptable practices of good animal husbandry were followed, per the Guide for Care and Use of Laboratory Animals, National Research Council. 1996.

Meteorological Data: Room temperature and humidity was recorded daily, however, measurements were not provided.

Ventilation/Air-Filtration: The facility was equipped with industrial fans to keep the air flowing.

2. Animal(s) Monitored:

Species/Breed: Beagle dog

Number of animals in study: 24 (3 dogs per treatment group)

Age: ≥ 8 weeks of age

Body weight: 20.3 to 34.8 lbs on Day -1

Feeding: Commercial rations of food were offered once daily. The animals were allowed ad libitum access to fresh potable tap water at all times. There were no known contaminants in the feed or water that could interfere with this study.

Health: No prophylactic or therapeutic drugs were administered to a test animal for at least 14 days prior to dosing. No concomitant medication was necessary during the course of the study. Each animal was observed a minimum of once daily by qualified personnel (e.g., veterinary technician) for clinical or behavioral abnormalities beginning at acclimation and continuing through the day following that animal's sample collection. The skin and hair at the application site was carefully examined for abnormalities on Day -1 prior to treatment, and at 24 and 48 hours post treatment.

Surface characteristics: Characteristics of the dog surface were not provided.

Other products used: Dogs received shampoo / washing (alcohol-based) prior to the study. Only dogs with no exposure within three months previous to the test substance or any other topical treatments were used.

3. Physical State of Formulation as Applied:

The test substance was a liquid spot-on formulation.

4. Application Rates and Regimes:

Application rate(s): All dogs were treated with 4 ml of the formulation, which is the label rate for dogs weighing 21 to 55 lbs. The weight of the applicator before and after dosing was recorded in grams. The amount of test substance was calculated based on the weight differences of the applicator tube. The total mass of test substance applied was between 4.25 and 4.56 g/dog. Adjusted for percent active ingredient (22% dinotefuran), the mass dinotefuran applied was 935 to 1003 mg ai/dog. Doses, based on individual body weights of each dog, ranged from 62.5 to 108 mg/kg.

Application Regime: All animals were treated once on Day 0 (November 2, 2011). Using the applicator tube held in an upright position, the test substance was applied evenly to three spots along the dog's back, beginning between the shoulder blades and continuing in the order shown in the diagram below (Figure 1), squeezing the applicator tube until empty. The hair was parted down to the level of the skin and the test substance was slowly applied, avoiding superficial application to the animal's hair. For two dogs, LGJ-6 and 1170768, it was noted that a small amount of formulation was observed running on the top hairs without loss, while two other dogs, PUT-0 and LHI-6, had approximately two drops of product run-off that was lost. For eleven dogs, the test substance was observed pooling at the application sites. The applicator for dog JAI-6 was noted as difficult to dispense and having some leakage at the collar (between the discs above the tip).

Figure 1: Location of Application Spots

Application Equipment: The test substance was applied using an applicator tube containing the test substance.

Human Safety: Gloves, apron and eye protection were worn while preparing and administering the doses.

5. Transferable Residue Sampling Procedures:

Method and Equipment: Dye-free 100% cotton gloves were used to collect residues. Three gloves were placed over a mannequin hand (Northwest Mannequin, Seattle, WA;Part Number Hand M2) and used for sampling. A nitrile glove was placed over the mannequin hand prior to the cotton gloves. The nitrile glove was changed between dogs to avoid cross-contamination.

Sampling Procedure(s): The sampler manipulated the prosthetic mannequin hand in order to mimic normal petting actions. One sample consisted of 30 petting simulations, with a simulation consisting of three strokes in the following order:

- One stroke on the right side (along the ribcage);
- One stroke on the left side (along the ribcage); and
- One stroke on the back line, including the application site.

The strokes were intended to cover the whole body surface from head to tail and were made with uniform pressure. The palmar surface of the gloved mannequin hand was used, with fingers splayed.

After the petting exercise, the sampler removed the cotton glove by grasping the glove at the wrist and pulling the glove off the mannequin hand. The cotton glove samples were placed directly into separate pre-labeled wide-mouth amber jars with Teflon lids and placed in a plastic bag.

Surface Area(s) Sampled: The surface area of the stroking area or the palmar surface area of the gloved hand performing the petting strokes was not provided.

Sampling Time: The length of time to complete a sample or petting simulation was not provided.

Replicates per surface:

- Replicates per sampling time: Three dogs were sampled at each interval.
- Number of sampling times: There were a total of 9 sampling intervals, including one sampling event prior to application.

Times of sampling: Samples were collected prior to treatment from all treatment groups and at intervals of 4 hours, 12 hrs, and 1, 2, 4, 7, 14 and 28 days post-application for separate treatment groups (treatment groups 1-8).

6. Sample Handling:

Immediately after collection the samples were placed on dry ice in a cooler. At the end of each sampling interval all samples were transported to the analytical laboratory (Golden Pacific Laboratories, LLC in Fresno, CA) in a cooler on dry ice. At the laboratory samples were stored frozen (temperature not provided) until analysis.

7. Analytical Methodology:

Extraction method(s): The glove samples were extracted with 200 ml of methanol and shaken for 15 minutes. A 1 mL aliquot of the methanol extract was added to 4 mL of a

20% acetonitrile / 80% water solution and shaken to mix. Samples having higher residue levels were diluted to an appropriate final volume, using a 20% acetonitrile / 80% water solution so that the response fell within the calibration range of the standards.

Detection method(s): Analysis was performed using HPLC/MS-MS. Table 1 presents a summary of the typical operating conditions.

Table 1. Summary of Typical HPLC/MS-MS Conditions

Instrument:	AB Sciex API 4000 with Turbo IonSpray
Column	Phenomenex, Luna 3 µ, C18(2), 100Å, 50 x 3.00 mm
Flow Rate	500 µL/min
Injection volume	Not reported
Mobile phase	A: acetonitrile B: 0.2% acetic acid in water
Gradient Program	Total Time (min) %A %B 0 0.0 100 5.0 50.0 50.0 5.01 0.0 100 7.0 0 100
Ionic transitions	Positive ions were monitored in MRM mode with Unit Resolution Dinotefuran m/z 203.00 (Q1) m/z 129.00 (Q3)
Retention Time	~2.7 minutes

Method validation: The analytical method GPL-MTH-073 was previously validated in cotton gloves in GPL Study 100338. As reported in GPL Study 100338, the overall average recovery of dinotefuran was 104% ± 2.87% at fortification levels of 0.999, 1000, and 10,000 µg/sample (n=7 per level).

The limit of quantitation (LOQ) for dinotefuran was reported as 1.0 µg/glove. A limit of detection (LOD) was not provided.

Instrument performance and calibration: Calibration curves are prepared from solvent standards. Calibration standards are injected at the beginning and end of an analytical set. The lowest level analytical standard corresponds to 70% or less of the limit of quantitation. A correlation coefficient (r) is calculated based on the standard concentrations and their respective peak area response. Correlation coefficients were greater than 0.9997.

Quantification: Quantitation of residues is determined from a calibration curve calculated using linear regression.

8. Quality Control:

Lab Recovery: Laboratory fortified samples were prepared at three levels: 1.0 µg/sample (n=4), 10,000 µg/sample (n=2), and 100,000 µg/sample (n=4). Recoveries ranged from

86.5 to 97.5%, with an overall average of 92.2±3.9%. No residues were detected above the LOQ in the laboratory control samples.

Table 2. Summary of Dinotefuran Laboratory Fortification Recoveries

Field Fortification Level (µg/sample)	n	Percent Recovery	Average	Standard Deviation
1	4	92, 92, 94, 87	91	3.2
10,000	2	97, 97	97	NA
100,000	2	87, 93	90	NA

Field blanks: Pretreatment background samples were collected from all dogs on Day -1, after shampoo/washing. Mannequin gloved hands were used to perform a single 3-stroke petting simulation set on each dog. No residues above the LOQ were detected in these samples.

Field recovery: Field fortification samples were **not** prepared.

Formulation: The Certificate of Analysis stated that the test product contained 22.21% dinotefuran.

Tank mix: Not applicable.

Travel Recovery: Travel recovery samples were not prepared.

Storage Stability: Cotton glove samples were stored frozen for 14 to 56 days after collection prior to analysis. A storage stability study was conducted as part of GPL Study 100338. Cotton glove samples were fortified with dinotefuran at 9.99 µg/sample and triplicate samples were analyzed at intervals of 0, 7, 14, 29, 91, and 182 days after frozen storage (<10 °C). Average storage stability recoveries, corrected for corresponding average laboratory recovery, were 101, 103, 100, 99, 102, and 95%, respectively. The storage stability results are adequate to demonstrate the stability of the dinotefuran in cotton glove samples stored frozen for up to ~6 months and support the storage conditions and durations of the cotton glove samples analyzed in this study.

II. RESULTS AND CALCULATIONS

Observations:

- For two dogs, LGJ-6 (day 1 treatment group) and 1170768 (4 hr treatment group), it was noted that a small amount of formulation was observed running on the top hairs without loss
- For two dogs, PUT-0 (day 1 treatment group) and LHI-6 (day 14 treatment group), approximately two drops of product run-off was lost.
- For eleven dogs, the test substance was observed pooling at the application sites.
- The applicator tube for dog JAI-6 (day 4 treatment group) was noted as difficult to dispense and having some leakage at the collar (between the discs above the tip).
- Dog No. CQI-6 (day 28 treatment group), sustained a small laceration to the left hind leg on Test Day 25. This was managed conservatively and the dog responded well with no complications. This is not considered an adverse event. No other abnormalities and no adverse findings were observed during the course of the study.

Calculations:
Measured dinotefuran residues per glove sample (µg/glove), total dinotefuran residue per dog surface area (µg/cm^2), and percent of applied dose transferred are shown in Table 3. A summary of these values are shown in Table 4. The Registrant did not correct the raw residue values. The dinotefuran residues were corrected by Versar using the average laboratory recovery from the fortification level closest to the field residue (91% for residues <5,000 µg/sample, 97% for residues 5,000 to 55,000 µg/sample, and 90% for residues >55,000 µg/sample). When residues were reported as less than the LOQ, Versar used a finite value of ½ LOQ (0.5 µg/glove) in calculations. Dinotefuran residues in µg/cm^2 of total dog surface area were determined by Versar using a dog surface area calculated using the following equation:

$$\textit{Surface area of dog (cm}^2\textit{)} = (12.3*((\textit{animal body weight (lbs)}*454)^{0.65}))$$

Additionally, Figure 2 is a graph of average percentage of applied dose that was determined to be transferable over time.

Average dinotefuran residue from petting simulations conducted 4 hours after application was 70,427 µg/glove (7.12% of applied dose). Residues decreased with increasing time between the test product application and dislodgeability sampling. At the Day 28 interval, the average dinotefuran residues were 500 µg/glove (0.05% of applied dose) and the inner glove residues were <LOQ.

Versar performed a dissipation kinetics analysis for dinotefuran based on the percentage of original application dose transferred, as natural logarithms. Using the individual data points for percentage of applied dose transferable vs. time for samples collected from 4 hours through day 28 after application, the half-life calculated by Versar was 4.2 days (R^2 = 0.858).

III. DISCUSSION

A. LIMITATIONS OF THE STUDY:

The following issues of concern are noted:

- The Study did not follow two of the recommendations outlined by EPA in the protocol review dated November 17, 2009 (D368147, 11/17/09, B. O'Keefe). Note that in an announcement on the Summit VetPharm (SVP) website, it was announced that in 2010 CEVA acquired Summit VetPharm LLC.
    - HED recommended that SVP include a petting simulation within the first hour after treatment; e.g. at 30 minutes after treatment for an acute/slick test. In the actual field study, the first petting simulation after dosing took place 4 hours after treatment. *Note: In a subsequent meeting with Summit VetPharm HED agreed to the first petting simulation occurring at 4 hours after treatment.*
    - HED recommended that SVP consider the dog's health and their ability to remove product residue in the label and protocol directions. As stated in the submitted protocol, "whenever possible, dosing should be restricted to areas that would be difficult for the dog to reach and generally inaccessible for grooming purposes (i.e., intrascapular). *Instead*, the application of test substance in the field took place at three spots along the dogs back (intrascapular to back of tail area). According to the HED protocol review "If applied at three spots, the dogs may be able to lick and remove the mid-back and base of

tail application points." *Note: In a subsequent meeting with Summit VetPharm HED agreed to allow the three spot application procedure.*

- The mannequin hand was clothed in three cotton gloves and one nitrile glove. Rinse samples of the chemical resistant gloves were not collected. Absorbency data were not presented to quantify transfer through the three cotton gloves or to examine the difference between cotton gloves and bare hands.

- Field fortification samples or travel recovery samples were not prepared. The Registrant did, however, submit a storage stability study (GPL Study 100338) which demonstrated the stability of dinotefuran in cotton glove samples for up to 6 months of frozen storage. Additionally, laboratory recovery samples were analyzed with each analytical set.

- The Registrant did not correct the residues for storage stability or laboratory recovery. Versar corrected the results for average laboratory recoveries.

- The characteristics of the mannequin hand were not reported, such as type of plastic and surface area.

- The amount of pressure applied to the mannequin hand was not reported.

- No information was provided on the fate of the product once it is applied. The samples were analyzed for dinotefuran only.

- The Submitter did not sign the GLP Compliance Statement of the Study Report.

B. <u>CONCLUSIONS</u>:

The Registrant did not correct residues for laboratory fortified sample recoveries. Therefore, the Versar calculated dinotefuran residues were slightly different from those calculated by the Registrant. The highest mean dinotefuran residue occurred at 4 hours after application (7.12% of applied dose) and declined with increasing sampling intervals (0.05% of applied dose by Day 28). The half-life calculated by Versar was 4.2 days ($r^2 = 0.86$) for the percentage of applied dose transferred. The Registrant's half-life was similar (4.2 days; $r^2 = 0.87$).

Table 3. Dinotefuran Residues from Cotton Gloves Following A Petting Simulation to Treated Dogs[a]

Interval After Application	Amount Dinotefuran Applied (µg ai)	Animal Weight (lb)	Surface Area of Dog[b] (cm^2)	Measured Dinotefuran Residue on Cotton Gloves (µg/glove)				Corrected Dinotefuran Residue on Cotton Gloves[c] (µg/glove)			Residue per surface area of dog (µg/cm^2) [d]			% of applied dose transferred[e]		
				Inner	Middle	Outside	Total	Total	Average	St. Dev.	Total	Average	St. Dev.	Total	Average	St. Dev.
4 Hours	992	25.8	5426	39.7	956	64,865	65,860.7	73,179	70,427	31,193	13.5	46.8	40.7	7.38	7.12	3.2
	994	26.2	1093	10	165	36,637	36,812	37,951			34.7			3.82		
	986	27.8	1087	384	2166	87,588	90,138	100,153			92.1			10.16		
12 Hours	988	34.8	1088	16.7	242	56,456	56,714.7	63,016	45,872	18,220	57.9	42.2	16.7	6.38	4.65	1.8
	986	31.7	1087	39.6	237	46,146	46,422.6	47,858			44.0			4.85		
	983	21.2	1085	19.9	192	25,726	25,937.9	26,740			24.7			2.72		
1 Day	986	25.6	1087	26.6	179	28,028	28,233.6	29,107	38,872	9,112	26.8	35.6	8.3	2.95	3.91	0.9
	990	22.0	1090	189	399	45,145	45,733	47,147			43.3			4.76		
	1003	22.0	1099	36.8	476	38,639	39,151.8	40,363			36.7			4.02		
2 Days	990	26.7	1090	13.5	252	26,527	26,792.5	27,621	31,057	3,118	25.3	28.6	2.9	2.79	3.15	0.3
	988	29.8	1088	18.6	244	32,432	32,694.6	33,706			31.0			3.41		
	977	23.6	1080	19.2	340	30,531	30,890.2	31,846			29.5			3.26		
4 Days	983	22.0	1085	7.43	177	12,062	12,246.43	12,625	17,145	5,914	11.6	16.0	5.9	1.28	1.78	0.7
	935	20.9	1050	378	373	22,372	23,123	23,838			22.7			2.55		
	997	20.3	1095	17.6	191	14,314	14,522.6	14,972			13.7			1.50		
7 Days	983	21.2	1085	4.57	44.1	18,719	18,767.67	19,348	9,536	8,785	17.8	8.79	8.1	1.97	0.97	0.9
	983	25.8	1085	40.4	156	6,456	6,652.4	6,858			6.3			0.70		
	983	22.9	1085	1.82	11.8	2,172	2,185.62	2,402			2.2			0.24		
14 Days	983	22.0	1085	1.48	20	3,008	3,029.48	3,329	7,877	5,367	3.1	7.22	4.9	0.34	0.79	0.5
	990	21.6	1090	9.76	43.1	6,256	6,308.86	6,504			6.0			0.66		
	994	23.6	1093	38.4	117	12,262	12,417.4	13,797			12.6			1.39		
28 Days	994	20.5	1093	<LOQ[f]	1.5	198	200	220	500	380	0.2	0.46	0.4	0.02	0.05	0.0
	975	22.0	1079	<LOQ[f]	2.12	846	848.62	933			0.9			0.10		
	983	22.3	1085	<LOQ[f]	3.98	312	316.48	348			0.3			0.04		

a. Dinotefuran residues transferred from dog hair treated with 4 mL of Ceva Animal Health Vectra for Dogs & Puppies™ (22% dinotefuran) to cotton gloves after stroking the dog ninety times (30 petting simulations of 3 strokes each) with a mannequin hand fitted with three cotton gloves over top of a nitrile glove. Each dog was sampled only once after application.
b. Surface area of dog (cm^2) = ((12.3*((Animal weight (lb)*454)^0.65))
c. Residues were corrected for the average laboratory fortification recovery from the fortification level closest to the field residue (refer to Table 2).
d. Residue per dog surface area (µg/cm^2) = corrected dinotefuran residue (µg/glove) / surface area of dog (cm^2).
e. % of applied dose transferred = corrected dinotefuran residue (µg/sample) / applied dose (µg) *100
f. LOQ = 1 µg/sample. ½ LOQ was used in calculations for residues <LOQ.

Table 4. Summary Dinotefurn Residues from Cotton Gloves Following Petting Simulations to Treated Dogs						
Interval After Application	Corrected µg/glove		µg/cm^2 body surface area of dog		% of applied dose transferred	
	Average	Standard Deviation	Average	Standard Deviation	Average	Standard Deviation
4 Hours	70,427	31,393	46.8	40.7	7.12	3.2
12 Hours	45,872	18,220	42.2	16.7	4.65	1.8
1 Day	38,872	9,112	35.6	8.3	3.91	0.9
2 Days	31,057	3,118	28.6	2.9	3.15	0.3
4 Days	17,145	5,914	16.0	5.9	1.78	0.7
7 Days	9,536	8,785	8.79	8.1	0.97	0.9
14 Days	7,877	5,367	7.22	4.9	0.79	0.5
28 Days	500	380	0.46	0.4	0.05	0.0

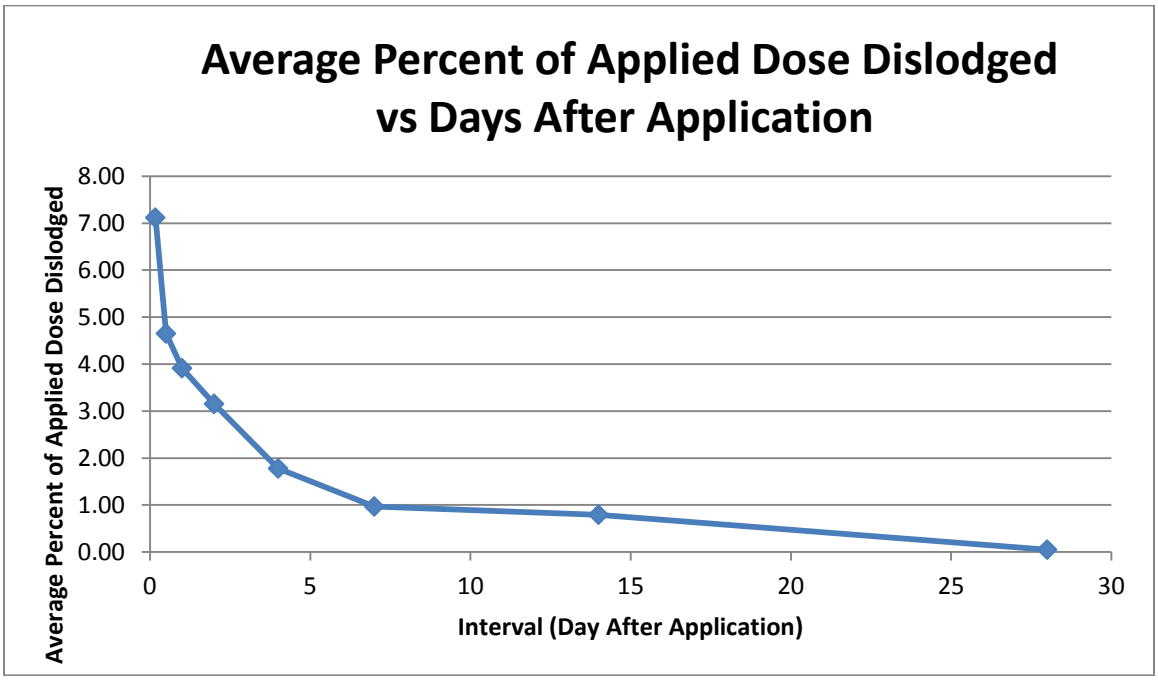

Figure 2. Percent of Applied Dose that was Transferred for Dinoefuran

Appendix A

Compliance Checklist

COMPLIANCE CHECKLIST

This compliance checklist is based on applicable criteria of the OPPTS Test Guidelines Series 875, Occupational and Residential Exposure Test Guidelines, Group B: 875.2300 (indoor surface residue) and OPPTS Test Guidelines Series 875, Occupational and Residential Exposure Test Guidelines, Group B: 875.2400 (dermal exposure).

- *The test substance must be the typical end use product of the active ingredient.* This criterion was met.

- *The production of metabolites, breakdown products, or the presence of contaminants of potential toxicologic concern, should be considered on a case-by-case basis.* This criterion was not met. The pharmacokinetics of dinotefuran was not reported. Samples were analyzed for dinotefuran only.

- *Indoor surface residue studies should be conducted under ambient conditions similar to those encountered during the intended use season, and should represent reasonable worst case conditions.* This criterion was met.

- *Ambient conditions (i.e., temperature, barometric pressure, ventilation) should be monitored.* This criterion was met.

- The *end use product should be applied by the application method recommended on the label.* This criterion was met.

- *The application rate used in the study should be provided and should be the maximum rate specified on the label. However, monitoring following application at a typical application rate is more appropriate in certain cases.* This criterion was met.

- *If multiple applications are made, the minimum allowable interval between applications should be used.* This criterion does not apply. Only one application was made.

- *Sampling should be sufficient to characterize the dissipation mechanisms of the compound (e.g., three half-lives or 72 hours after application, unless the compound has been found to fully dissipate in less time; for more persistent pesticides, longer sampling periods may be necessary). Sampling intervals may be relatively short in the beginning and lengthen as the study progresses. Background samples should be collected before application of the test substance occurs.* This criterion was met.

- *Triplicate, randomly collected samples should be collected at each sampling interval for each surface type.* This criterion was met. Three replicates were collected.

- *Samples should be collected using a suitable methodology (e.g., California Cloth Roller, Polyurethane Roller, Drag Sled, Coupons, Wipe Samples, Hand Press, vacuum cleaners for dust and debris, etc.) for indoor surfaces.* This criterion was met, as the methodology for sample collection was approved by EPA.

- *Samples should be stored in a manner that will minimize deterioration and loss of analytes between collection and analysis. Information on storage stability should be provided.* This criterion was met. Samples were stored frozen between collection and analysis.

- *Validated analytical methods of sufficient sensitivity are needed. Information on method efficiency (residue recovery), and limit of quantitation (LOQ) should be provided.* This criterion was met.

- *Information on recovery samples must be included in the Study Report. A complete set of field recoveries should consist of at least one blank control sample and three or more each of a low-level and high-level*

fortification. These fortifications should be in the range of anticipated residue levels in the field study. This criterion was not met. Field fortification samples were not prepared.

- *Raw residue data must be corrected for fortified recoveries less than 120%.* This criterion was not met. Dinotefuran residue samples were not corrected.

- *The monitoring period should be of sufficient duration to result in reasonable detectability on dosimeters. Monitoring should be conducted before residues have dissipated beyond the limit of quantification. Baseline samples should be collected before the exposure activity commences.* These criteria were met. Background samples were collected from each dog prior to application and were also analyzed.

- *Activities monitored must be clearly defined and representative of typical practice.* This criterion was partially met. The activity of stroking a dog is a typical post-application activity.

- *Sufficient control samples should be collected.* This criterion was partially met. Separate control groups were not monitored. Only background samples from each dog prior to sampling were collected.

Appendix B

Regression Analysis
(Percent of Original Application Rate Transferable vs. Time)

Regression Analysis: Summary Output for Petting Dogs

Regression Statistics	
Multiple R	0.929364
R Square	0.863717
Adjusted R^2	0.857523
Standard Error	0.61803
Observations	24

ANOVA

	df	*SS*	*MS*	*F*	*Signif. F*
Regression	1	53.25658	53.25658	139.42931	5.4155E-11
Residual	22	8.403146	0.381961		
Total	23	61.65973			

	Coeff.	*Std. Error*	*t Stat*	*P-value*	*Lower 95%*	*Upper 95%*
Intercept	1.479318	0.160498	9.217021	5.209E-09	1.146464278	1.812171195
Slope	-0.1654	0.014008	-11.808	5.416E-11	-0.194452024	-0.136352045

Half Life = 4.190681 Days

Predicted Concentration Levels

Time (Days)	Residue (% tranferability)
0	4.38995
1	3.720714
2	3.153502
3	2.67276
4	2.265305
5	1.919966
6	1.627273
7	1.3792
8	1.168945
9	0.990743
10	0.839707
11	0.711696
12	0.6032
13	0.511244
14	0.433306
15	0.36725
16	0.311264
17	0.263812
18	0.223595
19	0.189509
20	0.160619

Time (Days)	Residue (% tranferability)
21	0.1361327
22	0.1153797
23	0.0977904
24	0.0828825
25	0.0702473
26	0.0595383
27	0.0504619
28	0.0427691
29	0.0362491
30	0.030723
31	0.0260394
32	0.0220698
33	0.0187053
34	0.0158537
35	0.0134369

Regression Analysis: Means and CVs for Petting Dogs

Days after Last Treatment	Residues (% tranferability)	Mean (% tranferability)	Standard Deviation (% tranferability)	Coefficient of Variation (%)
0.166666667	7.38	7.12	3.18	44.6
	3.82			
	10.16			
0.5	6.38	4.65	1.84	39.5
	4.85			
	2.72			
1	2.95	3.91	0.91	23.3
	4.76			
	4.02			
2	2.79	3.15	0.324	10.3
	3.41			
	3.26			
4	1.28	1.78	0.677	38
	2.55			
	1.50			
7	1.97	0.97	0.894	92.1
	0.70			
	0.24			
14	0.34	0.795	0.538	67.7
	0.66			
	1.39			
28	0.02	0.051	0.0392	76.8
	0.10			
	0.04			

Regression Analysis: Log of Concentration vs. Time for Petting Dogs